Compliance and Quality

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Overview

- **Vision for Quality**
  - **Quality Focus for Industry**
  - **Recalls and Field Alert Reports (FARs)**
  - **Shortages**
  - **Quality Focus for FDA**
  - **New Contract Manufacturing Draft Guidance**
- **Food and Drug Administration Safety and Innovation Act (FDASIA)**

Quality Focus for Industry

A MAXIMALLY EFFICIENT, AGILE, FLEXIBLE PHARMACEUTICAL MANUFACTURING SECTOR THAT RELIABLY PRODUCES HIGH QUALITY DRUGS WITHOUT EXTENSIVE REGULATORY OVERSIGHT

Commitment to quality

- Essential… from the top down and bottom up
- Cannot settle on “meeting regulators standards”
  - Must meet ***YOUR*** standards to reliably produce high quality products
- Elements
  - proactively identify & promptly correct issues
  - design/qualify robust operations
  - maintain equipment and facilities
  - Implement robust quality management systems
- Significant impacts to the public’s health
  - Cost of poor quality – $$$$$$$$$$$$
  - Cost to patients – shortages, adverse events, etc.

How mature is your quality system?

Level 1: Small problems ultimately snowball into larger ones, and management becomes aware only when there is a crisis.

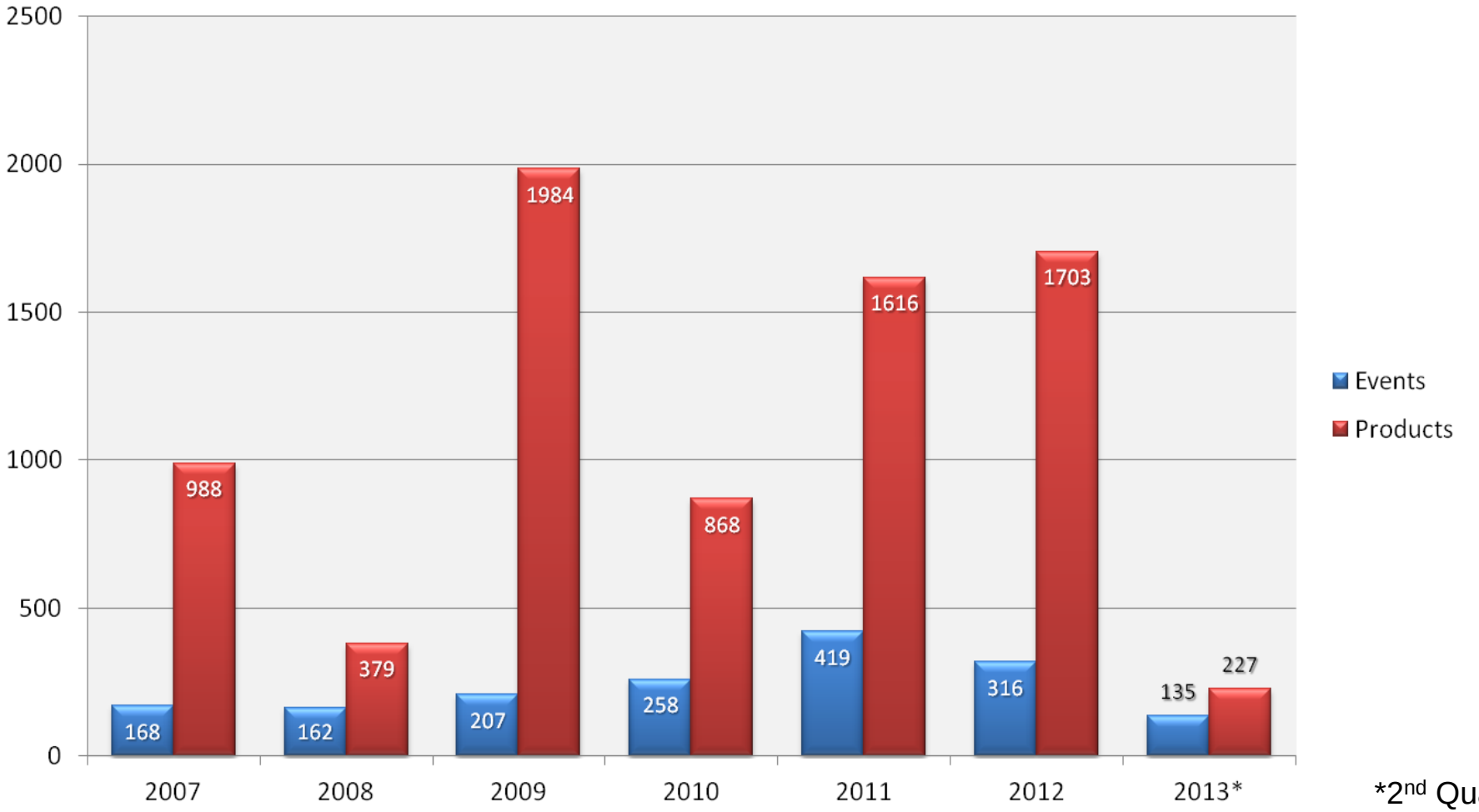
Level 2: Nearly always reactive, but there is willingness to change. Patchwork corrections are the norm.

Level 3: More proactive. Increasingly surfaces major issues and makes lasting systemic improvements.

Level 4: Routinely acts preventively, and institutionalizes (rewards) meaningful process and system improvements.

Recalls

Total Event vs Product Recalls FY 07-13*



*2nd Quarter

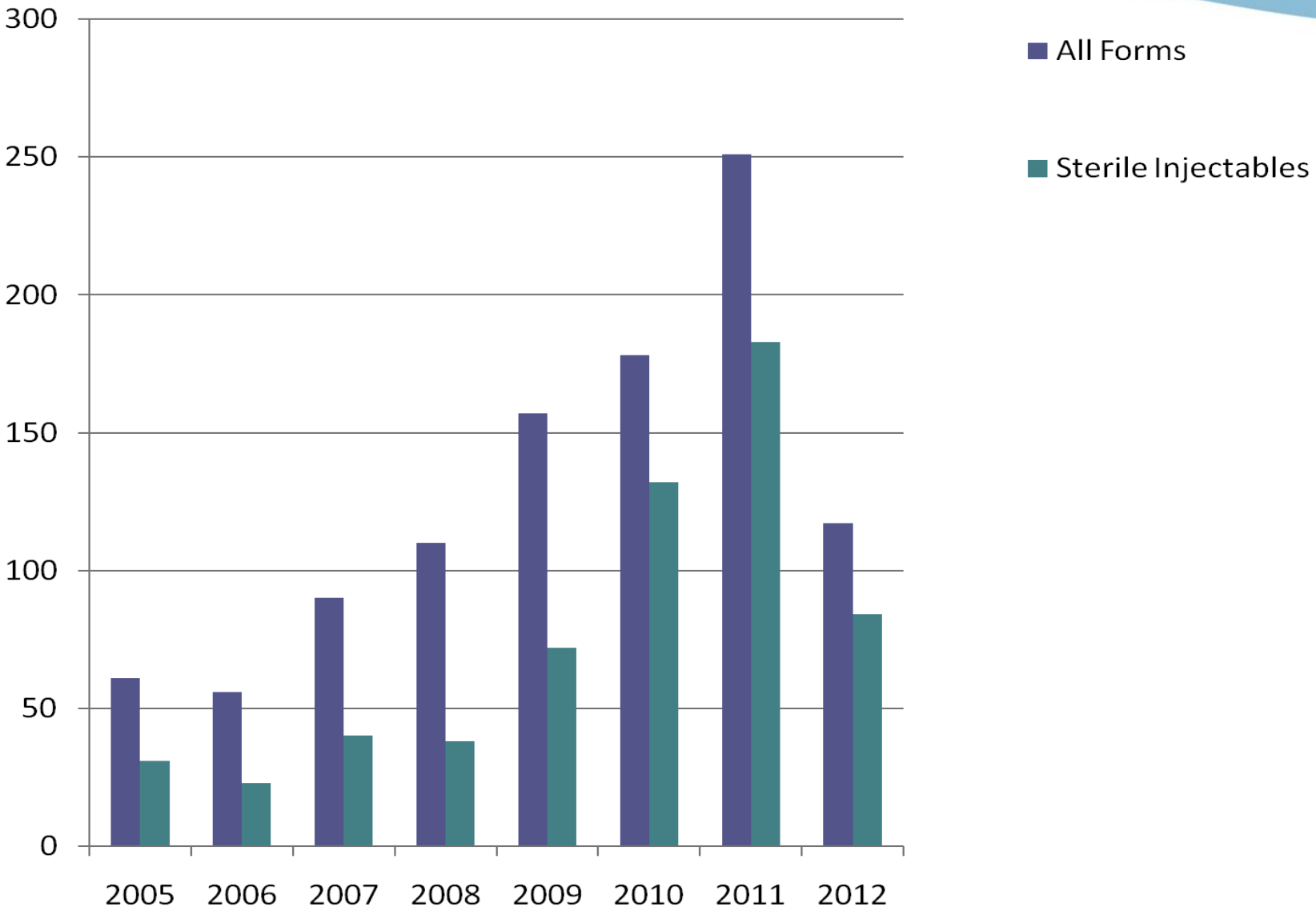
Major Reasons for Recalls FY 10-13*

2010	**Impurities Degradation Products** **GMP Deviations** **Marketed Without an Approved NDA/ANDA**
2011	**GMP Deviations** **Marketed without an Approved NDA/ANDA** **Impurities/Degradation Products**
2012	**Impurities/Degradation Products** **GMP Deviations** **Lack of Assurance of Sterility**
2013*	**Lack of Assurance of Sterility** **Impurities/Degradation Products** **Presence of Particulate Matter**

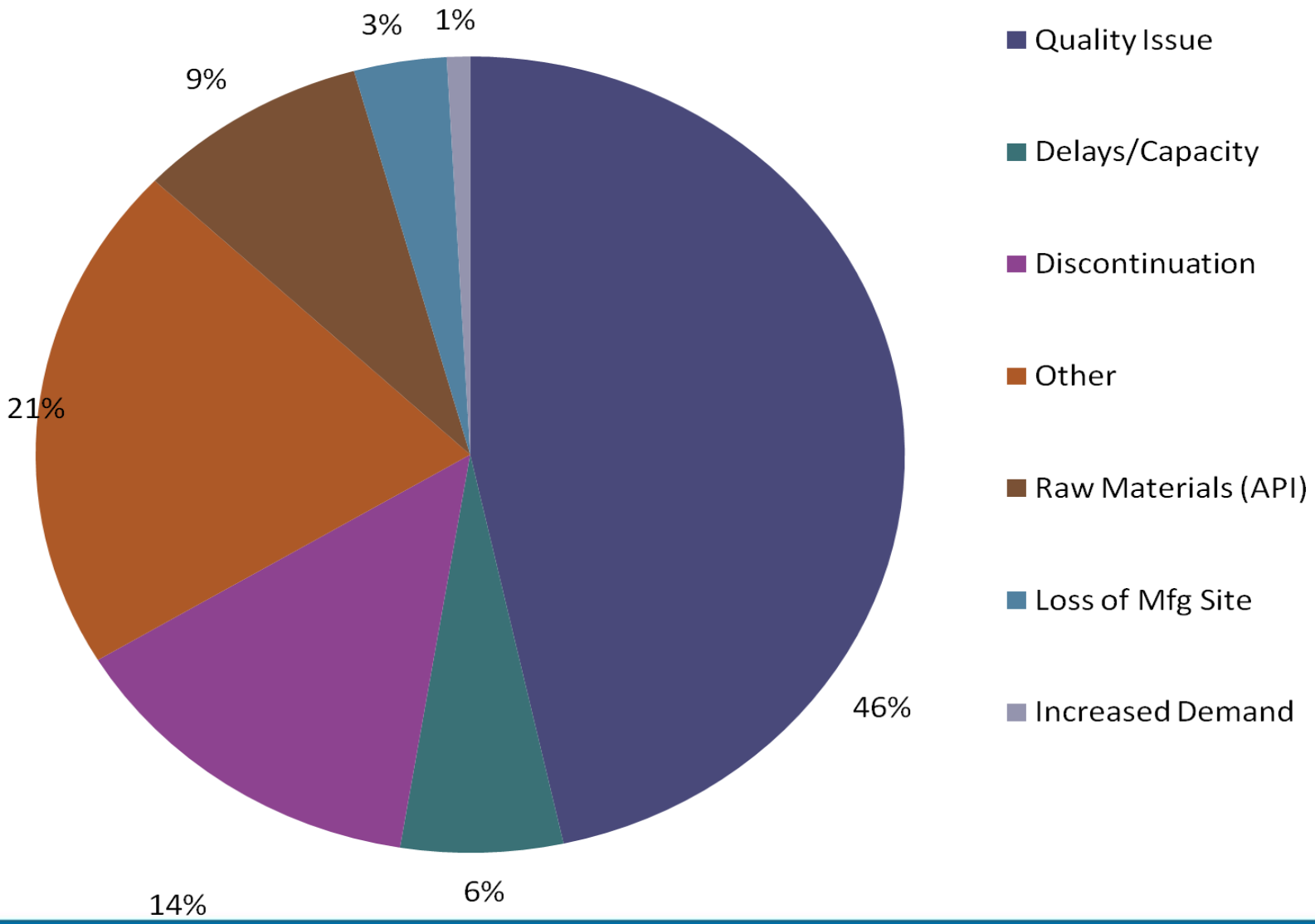
*2nd Quarter

Drug Shortages

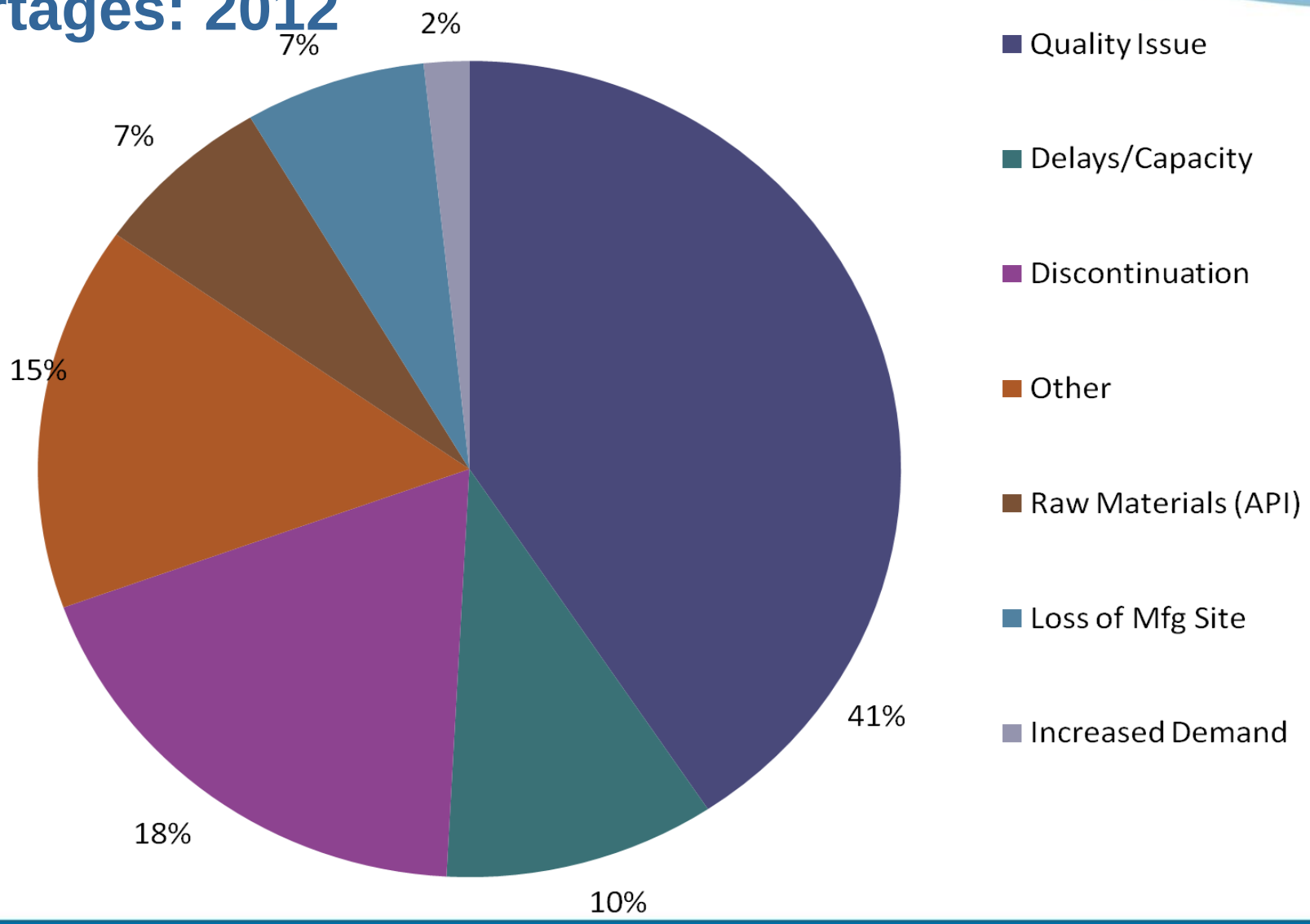
Total US drug shortages per year



Reasons for drug shortages: 2012

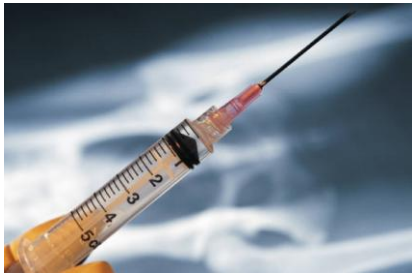


Reasons for sterile injectable drug shortages: 2012



Reasons for shortages: Sterile injectables

- Failure of quality management
- State of the industry
  - Seven (7) manufacturers make up most of market
  - Contract manufacturers – firms contract out manufacturing as well as acting as contract manufacturers
- Lack of redundancy
  - Multiple products made on existing manufacturing lines
  - 24/7 production with no “cushion”
- Complex manufacturing process
  - No simple fixes
  - Problems typically affect multiple products
- Investment economics question
  - e.g., propofol 20ml sells for $0.48/vial



FDA authorities are very limited

What we can require

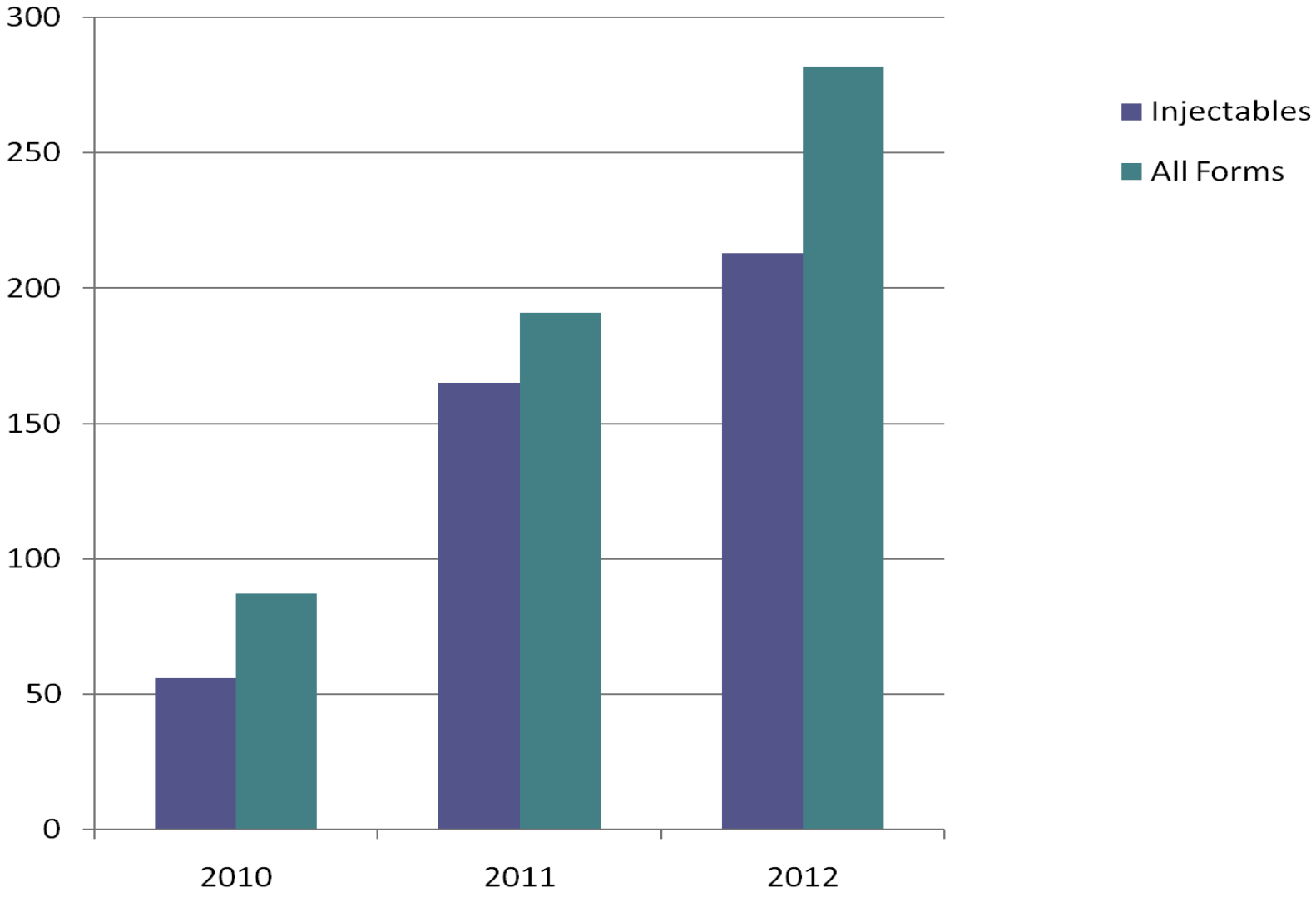
- Notification by sole source manufacturers*
  - Discontinuance of certain products
  - 6 months in advance or immediately if not foreseen
  - No penalty for not reporting
- Notification of manufacturing changes

What we can't require

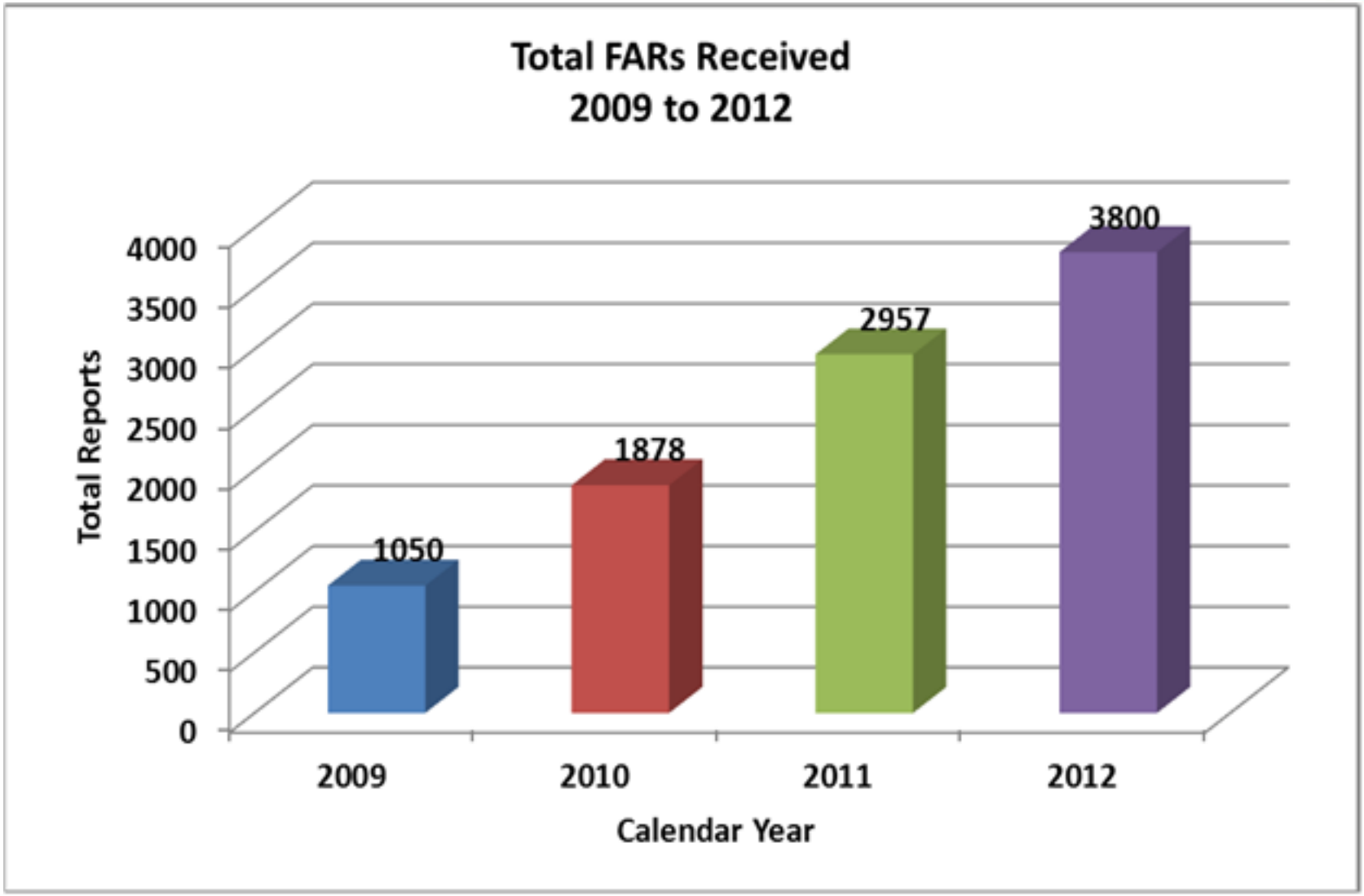
- A company to make a drug or make more
- Notification of all production delays for all products
- How much and to whom drug is sold or distributed

FDA drug shortages program largely depends on voluntary notification by manufacturers and the public.

Averted drug shortages: 2010-2012



Field Alert Reports (FARs)


Total FARs Received
2009 to 2012
Total Reports
4000
3500
3000
2500
2000
1500
1000
500
0
1050
1878
2957
3800
2009
2010
2011
2012
Calendar Year

FDA FAR Initiative

Current	Proposed future

• Multiple formats and methods of delivery for incoming FARs from firms
  • Pdf, Tif forms
  • Postal Mail
  • Fax
  • Email
• Firm reports sent to District Office and then to CDER
• No FAR numbering conventions
	• New Form uses Adobe PDF and Extensible Markup Language
	  • New submit button in form generates one e-mail for you
	• Allows simultaneous submission of FAR to ORA and CDER
	• Unique identification of each FAR

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm347604.htm

Quality Focus for FDA

Addressing emerging drug quality issues

- Focus on overall approach to quality
- Seeking comprehensive approach to change
- Elements of change
  - Organizational
  - Process
  - Policy
- Stakeholder input

Principles for change

- More clear standards for review and inspection
- More clear enforcement policies
- Same standards for all drugs: lifecycle approach
- Specialization and team review: integration of review and inspection for a quality assessment
- Clinically relevant standards
- Surveillance using quantitative metrics
  - Links with increased focus on clarity and clinical relevance
  - Links with development of compliance policy
- Overall QMS and evaluation system

New Contract Manufacturing Draft Guidance

Contract Manufacturing Guidance *Purpose*

- Outlines critical roles played by both Product Owners and Contracted Facilities
- Main focus is Quality Agreements, which should
  - define responsibilities
  - assure full CGMP conformance, and
  - consistently deliver safe and effective medicines
- Some critical elements of Quality agreement include:
  - Provision for Owners to evaluate and audit Contracted Facility
  - Mechanisms for timely notifications and communications

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM353925.pdf

Contract Manufacturing Guidance *Responsibilities*

- **Owners** are ultimately responsible for final approval or rejection of drug product (211.22(a))
  - Ultimately responsibility cannot be delegated to Contracted Facility or via a Quality Agreement

- **Contracted facility** is responsible for:
  - Meet GMPs for all operations it performs, including promptly evaluating and addressing manufacturing or quality problems
  - Ensuring an appropriate Quality Unit product disposition (e.g., release, reject) decision for each operation it performs

New Legislation – FDASIA

FDASIA-User Fees

- The first 4 titles relate to user fees:
  - Gives FDA authority to collect user fees from industry
  - Steady & reliable income to bring new products to market safely & quickly
    - Prescription Drug User Fee Amendments **(PDUFA)**
    - Medical Device User Fee Amendments **(MDUFA)**
    - Generic Drug User Fee Amendments **(GDUFA)**
    - Biosimilar Products User Fee Amendments **(BsUFA)**

Generic Drug User Fee Amendments

- Problems
  - ANDA backlog
  - Globalization
- Responses in GDUFA
  - GMP and bioequivalence ramp up
  - Fee structure for application and facilities
  - Movement to surveillance model with parity
- Implementation Issues
  - Facility self-identification and fee setting
  - Enforcement of GDUFA requirements

Title VII – Drug Supply Chain

Increased Risk Information

Registration (foreign & domestic) with UFI

Excipient information

Electronic system

Information exchange

Standards of admission for imported drugs

Registration of commercial importers

Notification

Enhanced Tools

Administrative destruction

Prohibit inspectional delay, limitation, denial, refusal

Administrative detention

Protection against intentional adulteration

Penalties for counterfeiting drugs

Extraterritorial jurisdiction

Global Supply Chain

Risk-based inspections

Records for inspection

Recognizing foreign govt. inspections

Enhancing safety and quality of drug supply / QMS

What's around the corner?

- Enhance collaborations with foreign regulators
  - Conducting inspections- GMP, GCP, BE, PV
  - Sharing inspectional information
- Implementation of FDASIA
- Compounding pharmacies
- Further secure drug supply chain
- CDER reorganization

Thank You!

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